

711017 (3/12/85)

Hamashima

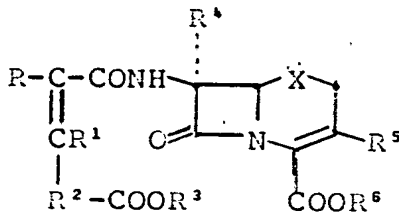
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WHAT WE CLAIM IS:

1. A 7beta-(carboxyalkenoylamino)-3-cephem-4-carboxylic acid compound represented by following formula and its derivatives:



(wherein R is aryl or a heterocyclic group;

R¹ is hydrogen or halogen;

R² is a single bond, alkylene, or thiaalkylene;

R³ is a hydrogen atom, salt forming atom or group, or ester forming group;

R⁴ is hydrogen or methoxy;

R⁵ is hydrogen or a 3-substituent of cephalosporins;

R⁶ is a hydrogen atom, salt forming atom or group, or ester forming group; and

X is oxygen, sulfur, or sulfinyl,

with the proviso that when R² is thiaalkylene, R¹ is halogen).

2. A compound claimed in Claim 1 wherein 7-acylamido double bond has amido and carboxylic substituents in cis position.

3. A compound claimed in Claim 1 wherein R is phenyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, or thiadiazolyl, especially that wherein R is optionally protected aminoisoxazolyl, aminothiazolyl, or aminothiadiazolyl.

4. A compound as claimed in Claim 1 wherein R is optionally

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protected aminothiazolyl.

5. A compound as claimed in Claim 1 wherein R¹ is hydrogen or chlorine.

6. A compound as claimed in Claim 1 wherein R² is optionally branched 1 to 3C alkylene.

7. A compound as claimed in Claim 1 wherein R⁴ is hydrogen.

8. A compound as claimed in Claim 1 wherein R⁵ is hydrogen, vinyl, cyanovinyl, trifluoropropenyl, acetoxymethyl, carbamoyloxymethyl, triazolylthiomethyl, methyltetrazolylthiomethyl, or thiadiazolylthiomethyl optionally substituted by amino, aminomethyl, or methyl.

9. A compound as claimed in Claim 1 wherein R³ and/or R⁶ is hydrogen, alkali metal, or a pharmacetically acceptable ester group. *

10. A compound as claimed in Claim 1 wherein R³ and/or R⁶ is an alkyl or aralkyl ester-forming group. *

11. A compound as claimed in Claim 1 wherein X is sulfur. *

12. A compound as claimed in Claim 1 that is one selected from the group consisting of : *

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-

3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-

3-methyl-3-cephem-4-carboxylic acid,

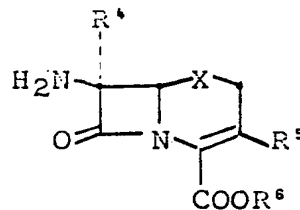
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-

3-vinyl-3-cephem-4-carboxylic acid,

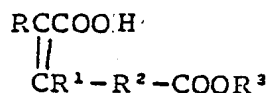
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-trifluoropropenyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-acetoxymethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-carbamoyloxymethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methoxymethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-pyridinioethyl-3-cephem-4-carboxylate,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-triazolylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-thiadiazolylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methyltetrazolylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methoxy-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-chloro-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-

3-fluoroethylthio-3-cephem-4-carboxylic acid,
 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
 3-trifluoroethylthio-3-cephem-4-carboxylic acid,
 7beta-[2-(2-aminothiazol-4-yl)-5-carboxy-2-pentenoylamino]-
 3-cephem-4-carboxylic acid,
 7beta-[2-(2-aminothiazol-4-yl)-6-carboxy-2-hexenoylamino]-
 3-cephem-4-carboxylic acid,
 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-pentenoylamino]-
 3-cephem-4-carboxylic acid,
 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-4-methyl-2-penten-
 oylamino]-3-cephem-4-carboxylic acid, and
 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-3-chloro-2-buten-
 oylamino]-3-cephem-4-carboxylic acid.
 and its salt and esters.

13. A process for preparing a compound as claimed in Claim 1
 which comprises amidating 7beta-amino-3-cephem-4-carboxylic
 acid derivative represented by the following formula:

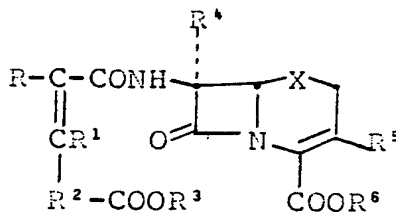


(wherein R⁴, R⁵, R⁶, and X are as defined in Claim 1)
 or its reactive derivative with carboxyalkenoic acid
 represented by the following formula:



(wherein R, R¹, R², and R³ are as defined in Claim 1) or its reactive derivative.

14. A process for preparing a salt as claimed in Claim 1 which comprises neutralizing a 7beta-(carboxyalkenoylamino)-3-cephem-4-carboxylic acid represented by the following formula:



(wherein R, R¹, R², R³, R⁴, R⁵, R⁶, and X are as defined in Claim 1 provided that at least one of R³ and R⁶ are hydrogen) or its reactive derivative with a base.

15. A process for preparing a compound as claimed in Claim 1 which comprises introducing a 3-function in a conventional manner selected from 3-double bond introduction by basic or thermal elimination of the corresponding 3-(hydroxy, acyloxy, or halo)cepham, sulfoxide reduction, reduction of 3-(halo or 3-sulfonyloxy)cephem, and displacement of 3-(leaving group-substituted)methyl-3-cephem with the corresponding nucleophilic reagent.

16. A process for preparing a compound as claimed in Claim 1 which comprises deprotecting a protected amino or protected carboxy of protected 7beta-(carboxyalkenoylamino)-3-cephem-

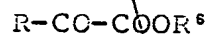
optionally branched alkylene.

23. A compound as claimed in Claim 22 wherein R^2 is methylene.

24. A compound as claimed in Claim 19 wherein R^3 is hydrogen, methyl, t-butyl, benzyl, methylbenzyl, p-methoxybenzyl, or p-nitrobenzyl.

25. A compound as claimed in Claim 19 wherein R^6 is hydrogen, diphenylmethyl, or p-methoxybenzyl.

26. A process for preparing a compound as claimed in Claim 19, which comprises subjecting an oxalate of the following formula:



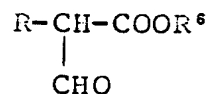
(wherein R and R^6 are as defined in Claim 1) to the Wittig type reaction by treating with an alkylidene-phosphorane of the following formula:



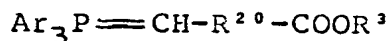
(wherein R^1 , R^2 , and R^3 are as defined in Claim 1 and Ar is aryl)

in an inert solvent at 50°C to 120°C for 10 minutes to 10 hours.

27. A process for preparing a compound as claimed in Claim 19, which comprises subjecting a formyl oxalate of the following formula:



(wherein R and R⁶ are as defined in Claim 1)
or its acetal to the Wittig type reaction by treating with an
alkylidenephosphorane of the following formula:



(wherein Ar and R³ are as defined in Claim 26, and R²⁰ is a
single bond or 1 to 3C alkylene)

in an inert solvent at 50°C to 120°C for 10 minutes to 10
hours.

28. A process for preparing a compound as claimed in Claim
19, which comprises deprotecting the carboxy-protecting group
R³ or R⁶ to give a compound of the following formula:



(wherein R, R¹, R² are as defined in Claim 1, and one or both
of R³ and R⁶ are hydrogen)

by treating with acid, Lewis acid and cation scavenger, base,
or hydrogen and catalyst in an inert solvent at -50°C to 100°C
for 1/6 to 10 hours.